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Negotiating Pharma Collaboration Agreements: Common and Critical Issues

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In recent years, pharmaceutical and biotechnology companies that sell products increasingly have made the strategic decision to externalize a significant portion of their drug discovery and development process by entering collaborations with smaller companies that focus on discovery, pre-clinical, and early-stage clinical development projects.[1] The parties enter often complex collaboration agreements that focus on specific therapeutic areas; reflect the parties' business needs and expertise; and define their roles and responsibilities in, and funding for, the collaboration and collaboration-related activities. The agreements also provide for the division of any economic benefits derived from the collaboration over time.

These types of collaborations typically provide that the smaller collaborator will take the lead responsibility in performing drug discovery and early-stage development, subject to varying levels of oversight and input from the larger collaborator, and that the larger collaborator will generally provide the smaller collaborator with funding for the work in the form of up-front and/or ongoing regular payments, as well as additional development milestone, or achievement, payments upon the successful completion of specific project goals.[2] The collaboration agreement typically will specify at what point or points in the development the larger collaborator is to assume primary responsibility for the project's continued development. If a project reaches that point, responsibility for continuing work will shift to the larger collaborator; under the collaboration agreement, it will continue to fund the project's development and will have ongoing responsibility for the later-stage development and the ultimate marketing of any approved product. Even after the smaller collaborator is no longer primarily responsible for a project's development, it may negotiate continued receipt of milestone payments under the collaboration agreement if the project progresses, as well as receipt of royalties on any sales of marketed products.

Because the collaborators have very different resources, corporate priorities, and perspectives on development, they often will have very different opinions of

[1] Patrick McGee, ''Pharma, Biotech Allies Replenish Pipeline,'' *PharmaAsia*, http://www.pharmaasia.com/article-5917-pharmabiotechalliesreplenishpipeline-Asia.html, March 12, 2011.

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[2] PharmaLive, ''M&A, Partnerships and Collaborations: Review of 2010 and Outlook,'' http://www.pharmalive.com/special_reports/sample.cfm?reportID=334, March 12, 2011.

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how to structure critical aspects of the collaboration to maximize and protect their respective interests. Although each collaboration has its own distinct dynamic, this article reviews, from the perspectives of both parties, the issues that are common and critical to the negotiation of collaboration agreements:

- Determining the collaborators' rights to various types of intellectual property related to the collaboration;
- Establishing effective governance mechanisms for the collaboration;
- Establishing rules to deal with targets, indications, and candidates that the collaborators will work on;
- Establishing exclusivity arrangements between the parties with respect to the collaboration efforts; and
- Negotiating the collaborators' indemnification and insurance obligations to each other as programs mature and respective responsibilities within the collaboration change.

Determining Intellectual Property Rights

The principal goal of collaborations is the development of intellectual property assets that will create value for the collaborators. The collaborators seek to discover and develop product candidates that have secure intellectual property foundations and become marketed drugs. Because intellectual property is the principal asset to be created by the collaboration, there are many complex intellectual property issues for the collaborators to consider when they negotiate a collaboration agreement.

Foremost is how to determine ownership of intellectual property developed in the course of the collaboration. The general legal principle is that, absent any contractual agreement to the contrary, the party that invents or discovers intellectual property owns it. There are many categories of intellectual property that may be involved in a collaboration, and the collaborators need to determine contractual rules to govern all of them. First, there is the pre-existing intellectual property that each party may bring to the collaboration to be utilized in it. In this case, the party that invented or discovered the intellectual property did so outside of the collaboration and before the collaboration came into existence. The inventing party will want to retain ownership of this type of intellectual property, but it will negotiate to provide the collaboration an adequate license to use the intellectual property during the collaboration term for purposes consistent with the aims of the collaboration, as well as in connection with any collaboration products that are taken to market.

The second category of intellectual property with which the collaborators will need to deal is the intellectual property developed within the collaboration. That intellectual property may be individually or jointly invented, depending on the level of involvement of each collaborator in its generation. The collaborators will negotiate the ownership of this type of intellectual property to ensure that the owner, or owners if there is joint inventorship, will provide an adequate license to the collaboration to utilize the intellectual property effectively.

An often sensitive issue arising in negotiations is ownership of improvements made to a party's pre-existing intellectual property in the course of the collaboration. The owner of the pre-existing intellectual property generally will want to own any improvements to such property, even if developed solely by the other party, because of the risks that the other party to the collaboration will seek to obtain blocking patents claiming obvious improvements to the pre-existing property or to work with a third party. This issue becomes particularly acute when a party's platform or manufacturing technology is involved. The parties can address these concerns by allocating ownership of improvements made to a party's pre-existing intellectual property to that party, while providing the developing party with an appropriately favorable license in recognition of its contribution to development of the improvement.

In many cases, parties will simply choose to jointly own intellectual property developed in the course of a collaboration, principally because joint ownership, from a business perspective, seems ''fair'' and ''reasonable.'' From a legal perspective, however, joint ownership creates a number of challenges. Joint owners default rights differ from country to country, and rules differ for different forms of intellectual property. Examples of these rules include the requirement in some countries that all joint owners join in any lawsuit to enforce a jointly owned patent, or that all joint owners approve any decisions regarding the licensing of a jointly owned patent or copyright. While many of these attendant issues can be addressed by a specific and carefully constructed agreement between the joint owners, enforceability of such agreements against bona fide purchasers and licensees could, in certain circumstances, be problematic. Accordingly, parties to a collaboration agreement should seek to avoid these issues altogether through the use of structural alternatives to joint ownership such as allocation of ownership by field of use, derivatives/improvements, and territory.

Working With a Patent Committee

In addition to allocating ownership of developed intellectual property, the parties will also want to negotiate control over prosecution strategy and implementation regarding intellectual property developed in the collaboration. One contractual device that collaborators often use to frame their oversight of intellectual property related to collaboration programs is a patent committee. Typically comprising representatives of both parties, the committee is tasked with considering and deciding key prosecution matters, including when and in which jurisdictions to file for patents and maintain intellectual property and how to respond to comments on patent filings from regulatory authorities. Often the smaller collaborator will negotiate to retain the right to prosecute and maintain intellectual property during the time the particular project to which the intellectual property relates remains under its development. That collaborator also will often bear certain costs associated with the intellectual property's initial prosecution and maintenance.

The parties may negotiate a list of jurisdictions in which intellectual property is required to be prosecuted and allow the larger collaborator to decide, on a case-by-case basis, whether to add, at its cost, additional jurisdictions to the prosecution strategy. The parties also may negotiate that some or all prosecution and maintenance costs incurred by the smaller collaborator for a project will be reimbursed once the larger collaborator assumes development responsibility. In that scenario,

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after a project is turned over to the larger collaborator, that collaborator will assume control over, and responsibility for the costs of, prosecution and maintenance. However, irrespective of which party controls prosecution of co-developed intellectual property at a given time, the non-controlling party will desire the right to review in advance and comment on prosecution materials, and will negotiate time periods and processes by which those rights are to be effected. Often this review-and-comment process can be handled through the patent committee.

The parties also will need to decide which will have the right to enforce intellectual property if a potential or alleged infringement arises and, as in the discussions of which party ultimately controls prosecution, which will bear the enforcement costs. If the parties negotiate that the party primarily in charge of development of a project related to the intellectual property to be enforced will control enforcement strategy (subject to an obligation to consult with the other party), control over prosecution and enforcement will be aligned. Agreements customarily provide that if the party with the right to enforce intellectual property decides not to do so, it will so notify the other party, which will then have the right, at its option, to take up the enforcement and be responsible for the associated costs.

Of course, issues of standing need to be considered when allocating enforcement rights to intellectual property. For example, in the United States, a party having only a non-exclusive license under a patent generally has no right to bring a lawsuit to enforce that patent. Similarly, exclusive licensees in many cases may be required to join the patent owner in any patent enforcement lawsuit. Other issues may arise in connection with enforcement of pre-existing intellectual property relevant to the collaboration. The intellectual property owner may be reluctant to cede control of enforcement of pre-existing intellectual property to a collaborator because of the risk that the validity of the intellectual property may be challenged by the defendant in an enforcement action. In such cases, the parties may elect to allocate enforcement rights differently for pre-existing intellectual property as compared to intellectual property developed under the collaboration.

An additional important issue that collaborators will negotiate is their respective publication and disclosure rights concerning information generated in the collaboration. Each party will have to balance its desire to disclose progress in research and development activities with the need of the other party, and of the collaborative entity itself, to maintain confidentiality for strategic, competitive, or other legitimate reasons. A party may desire the right to make these types of disclosures to various audiences, such as academia, industry, or the investment community. The collaborators' perspectives on the necessity and extent of disclosure may be different. For example, individual collaboration projects (and the collaboration itself) may be more important, or material, to the smaller collaborator's business and prospects than to the larger collaborator's. For this reason, the smaller collaborator may want to make disclosures that are more frequent and go into greater detail about individual collaboration projects than the larger collaborator would customarily make in the ordinary cause of its business.

Collaboration agreements typically include provisions providing for advance review and approval of one party's proposed publications or presentations by the other party. The parties will negotiate specific time periods during which (1) the review will occur and (2) the reviewing party will be required to make any objections or comments. If the reviewing party objects to or comments on the proposed publication or presentation, the two parties will then discuss the objections or comments in an attempt to reach agreement on how to proceed. If the parties are unable to reach agreement, contractual provisions in the collaboration agreement will provide for a dispute escalation path as follows: collaboration governance body, then higher-ranking employees of each collaborator, or a neutral third party.

Establishing Appropriate Governance Mechanisms

The collaborative model contemplates both parties interacting to design and progress discovery and development programs. One of the most important topics parties will negotiate when establishing a collaboration is a contractual framework for managing both their interactions and the work to be performed. One contractual mechanism that collaborators often use to manage their interactions is a joint steering committee.

A joint steering committee typically comprises members nominated by, and representing, each collaborator. After the larger collaborator takes over primary responsibility for progressing a program, the smaller collaborator generally has significantly less input into the program, and the joint steering committee may even be dissolved and replaced with an obligation on the part of the larger collaborator to keep the smaller collaborator informed about program developments. The joint steering committee generally has review and oversight responsibilities for the research and development performed under the collaboration during the portion of the collaboration term when the smaller company takes the lead in performing those activities. The committee will have the authority to select and assign relative priority to collaboration programs and resources. In early-stage discovery collaborations, the committee may have the authority to evaluate and select targets to be pursued, programs (such as screening programs) to be utilized in the pursuit of each target, and assays and reagents to be utilized for each target. For more advanced stages of a collaboration, the committee may establish tractable hit criteria, lead declaration criteria, candidate selection criteria, and, ultimately, clinical proof-of-concept compound criteria for each program. The committee also may establish work plans (annual or multi-year) for collaboration programs, and serve as the body that formally considers and determines whether program objectives or milestones have been achieved. The committee can be empowered to establish subcommittees to consider discrete topics and report back to it, such as forming a patent subcommittee to focus on intellectual property matters.

Joint steering committees are typically chartered to meet at regular intervals. Meeting locations can alternate between the parties' facilities. Both parties will have input into the agenda for each committee meeting and the opportunity to prepare or add comments to draft minutes of the committee meetings.

An important issue to be negotiated is how the joint steering committee will make decisions. For a baseline rule, the parties may structure the governance such that the committee's decisions shall be made by unanimous vote of its members. The parties will need to negotiate

a resolution regime for times when the members do not agree. A common approach to resolving stalemates is to refer them to a senior ranking person at each party (in the case of the smaller company, a high-ranking corporate officer, and in the case of the larger company, someone with authority over the relationship) for discussion and resolution. Specific time periods during which points of disagreement will be referred from the committee, considered by the parties' designees, and resolved also need to be negotiated up front. If the parties cannot timely resolve the matter, there are a number of contractual possibilities that can be employed. First, the parties can agree that there are certain categories of decisions over which one party will have a ''tie-breaking'' vote. These categories can include budgetary matters, so that the party that would be required to expend funds cannot be forced to do so without its agreement. Alternatively, the parties can agree that certain categories of decisions be submitted to an outside expert, or panel of experts, to consider. If there is to be one expert, the parties will need to agree upon who it will be. If there is to be a panel, each party can select one expert with the third being selected jointly. As with consideration of unresolved issues by the parties' senior ranking persons, the specific time periods within which the expert or panel of experts must be selected and matters considered and resolved also need to be agreed upon.

Target, Indication, and Drug Candidate Rules

The scope of the collaboration should be specifically defined, focusing on which targets and indications will be covered and how drug candidates will be selected and moved forward. To enhance the prospects for successfully identifying viable drug candidates, the parties will want to focus their efforts on defined areas. In addition, the parties may have budget and resource constraints for the collaboration that would preclude its engaging in open-ended efforts. A specifically defined scope also facilitates budget and planning activities for the collaborators. That said, every collaboration agreement should allow for flexibility in adjusting targets, indications, and other goals as dictated by the results of early discovery and development activities. While this flexibility is typically built into the oversight authority provided to the joint development committee, the parties may also pre-agree to a number of backup targets and indications that can be pursued at the election of either party in the event that the results for the primary targets and indications are found to be less than satisfactory.

In many collaborations, a party (typically the smaller collaborator) will bring to the collaboration a specific drug candidate for further development and testing. In others, a party may have a suite of compounds that have been preliminarily screened but not fully assessed as to their suitability for development purposes. The collaboration agreement should take into account the possibility that a primary drug candidate is determined during the collaboration activities to be unsuitable for development. In such cases, one collaborator may give the other an option to select a backup candidate for further development, whether from a pre-existing suite of compounds controlled by the parties before the collaboration began or from compounds developed during discovery activities under the collaboration. The parties will typically want to have at least one backup candidate identified before the collaboration begins, particularly if the primary candidate is very early stage.

Exclusivity

The parties in a collaboration will want specifically to address the exclusivity of their collaboration efforts. A collaborator also will want assurances from the other collaborator that it will focus its efforts on the collaboration, and will not engage in competing activities. In addition, each party will want to minimize the possibility that the other will take knowledge garnered in the collaboration and use it to develop programs outside of the collaboration, thereby depriving the other of the expected benefits of the collaboration. Consider, for example, a collaboration that is focused on a specific target indication. Collaborator A may want to work on programs focusing on the target indication both within and outside the collaboration, and in fact may have pre-existing programs involving that target indication. Collaborator B, however, may want to limit the ability of Collaborator A to work on programs focusing on the target indication on its own or with other parties during and after the conclusion of the collaboration term. Collaborator B may therefore argue that during the collaboration term, Collaborator A should work only on programs focusing on the target indication. Collaborator B also may require that Collaborator A be ''locked up'' for a defined period of time after the conclusion of the first collaborator's work, i.e., prevented from working on programs focusing on the target indication that was part of the collaboration. While one or both of the collaborating parties may desire a broad exclusivity arrangement, the proposed structure should be reviewed by an attorney for antitrust and competition law issues.

Termination Issues

All collaborations will end at some point. The term of the collaboration typically will be defined for a specified number of years, at which point either the parties' relationship will end (because no suitable drug candidates were developed) or the focus will shift to commercialization of one or more drug candidates, typically for the life of any licensed or collaboration patents. A collaboration can, however, terminate prior to the parties' expectations for other reasons, such as a party's breach of the collaboration agreement or a party's insolvency. Effective structuring of any collaboration requires planning for both success and failure, occurring during both the term and post-term of the collaboration. Different reasons for termination (e.g., breach vs. failure to discover suitable drug candidates) may merit different treatment of the parties' rights and obligations, a subject for another article. At a minimum, however, the collaboration agreement should address the following termination-related issues: allocation of IP rights upon termination, allocation of any regulatory filings made for drug candidates, continuing needs regarding the licensing of pre-existing intellectual property, activities that were subject to oversight of the collaboration's intellectual property committee, and the wind-down of any extant development activities, particularly clinical trials.

Indemnification and Insurance Obligations

An additional concept that the parties to a collaboration will expend significant energy negotiating concerns their obligations to indemnify each other for dam-

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ages related to the collaboration and its programs. The parties will discuss the appropriate standard by which to evaluate when an obligation to indemnify arises. Possible standards include gross negligence, mere negligence, recklessness, and willful misconduct. The standard or standards the parties negotiate will typically apply to acts or omissions of the parties, their affiliates, and their respective officers, directors, employees, and agents in connection with the performance of obligations or the exercise of rights under the collaboration agreement. Indemnification obligations typically will also come into play with respect to damages based upon the breach of a representation, warranty, or covenant made by a collaborator under the collaboration agreement in connection with the research, development, manufacture, use, handling, storage, commercialization, and sale or other disposition of collaboration compounds or products for which the party has responsibility under the collaboration. Whatever the trigger, an obligation to indemnify can be vitiated if the other party's conduct led to the damages at issue.

Each party will want to ensure, through covenants to be included in the collaboration agreement, that the other has sufficient insurance to cover any claims that may be brought in connection with activities and obligations of the other under the collaboration. As collaboration programs progress through discovery and development, the amount of insurance the smaller company is required to maintain will also increase. Typically, the amount of minimum insurance coverage required of the smaller company increases as the work it performs on collaboration programs progresses from preclinical/phase I clinical development to phase II clinical development to phase III clinical development. The larger company may be self-insured and will provide a representation to that effect to the smaller company. Each company will typically be required to provide, upon request of the other, evidence they are carrying the requisite insurance under the terms of the collaboration agreement.

Conclusion

Collaborations between pharmaceutical and biotech often raise complex business and legal issues, which should be considered and addressed early on in the negotiations between the parties. Rather than relying on ''off-the-shelf'' documentation, the parties should clearly identify and document their business and strategic goals so that the collaboration agreement is appropriately tailored to maximize the value received by each of the collaborators, while clearly allocating roles, responsibilities and risks that may be associated with the collaboration. A collaboration agreement that directly and clearly addresses these issues will benefit the parties over the course of what in many cases will be a long-term relationship.